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APPLICATION NUMBER:

201153Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	16 December 2010, revised 28 January 2011
From	Jill Lindstrom, MD FAAD
Subject	Cross-Discipline Team Leader Review
NDA#-Supplement#	201153 (reference 22-483/001)
Applicant	Graceway Pharmaceuticals, LLC
Date of Submission	8 February 2010
PDUFA Goal Date	8 December 2010
Proprietary Name	ZYCLARA ALDARA
Established (USAN) names	imiquimod
Dosage forms / Strength	Cream/3.75% Cream/5%
Proposed Indication	external genital and perianal warts
Approved Indication	1. actinic keratoses (3.75%, 5%) 2. superficial basal cell carcinoma (5%) 3. external genital and perianal warts (5%)
Recommended:	<i>Complete Response</i>

1. Introduction

ZYCLARA (imiquimod) Cream, 3.75%, is a topical drug product for which the applicant seeks approval under Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act for the topical treatment of external genital and perianal warts (EGW)/condyloma acuminata in patients 12 years or older. This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

Imiquimod, an imidazoquinoline amine, is thought to be a toll-like receptor agonist that acts on TLR7 and induces the production of various cytokines including interferon alpha, interleukin-12, and tumor necrosis factor-alpha. The applicant currently markets two strengths of imiquimod cream: a 5% strength (tradename ALDARA) and a 3.75% strength (tradename ZYCLARA). The 5% strength product received approval for the treatment of external genital and perianal warts (EGW) in 1997, and subsequently received approval for the treatment of actinic keratoses (AK) in March 2004 and superficial basal cell carcinoma (sBCC) in July 2004. The 3.75% strength product received approval for the indication of AK in March 2010.

EGW are a sexually transmitted disease. The lesions are a clinical manifestation of infection with the human papilloma virus (HPV), a non-enveloped, double-stranded DNA virus of which there are more than 80 known genotypes. HPV 6 and 11 are genotypes most commonly associated with EGW, although other types have been implicated as well (including 16, 18, 31,

33 and 35, genotypes associated with neoplasia). The virus infects the basal layer of the epithelium, where it can exist in a clinically non-apparent latent state. It replicates in epithelial cells, and can produce exophytic papules and plaques which are clinically recognized as EGW. Transmission of HPV is thought to be facilitated by the presence of EGW lesions, and consequently treatment of the lesions may decrease infectivity. In the CDC *Sexually Transmitted Diseases Treatment Guidelines, 2010*, CDC states that treatment of EGW, "...can induce wart-free periods," and that treatment "...likely reduce[s], but probably do[es] not eradicate, HPV infectivity." Similar to the case with genital herpes outbreaks, treatment of EGW may reduce viral DNA even though it does not eradicate the virus. Treatment options for EGW include approved drugs (imiquimod cream 5%, podofilox solution 0.5%, sinecatechins ointment 15%, and interferon alpha-n3 [recurring or refractory EGW]), and mechanical therapies (liquid nitrogen cryotherapy, surgical excision, laser ablation)¹.

The labeled dosing regimen of imiquimod 5% cream in the treatment of EGW is application three times weekly for up to sixteen weeks until clearance of warts. The dosing regimen proposed in this application is application of up to one packet of the 3.75% cream daily for up to eight weeks until clearance of warts. The applicant indicates that their rationale for development of the new dosing regimen is, "... to address physician and patient needs to treat EGW in a shorter time with a simpler dosing schedule." They further state, "[t]he new 3.75% imiquimod product contains the same active moiety but is an optimal EGW treatment that possesses a significantly shortened duration of treatment with a simplified dose schedule (daily)."

The applicant was requested to study both regimens to provide safety and efficacy data for the treatment of EGW with both their marketed 5% cream and their proposed 3.75% cream, but did not do so. Thus the basis for the applicant's statement that the proposed treatment is optimal with regard to safety, efficacy, compliance, or convenience is not clear. The "significantly shortened duration" may be limited to the outliers (with 3.75%) and non-responders (with 5%), as both regimens prescribe treatment only until clearance (albeit with different maximum durations), and relative data on time to clearance was not provided. Additionally, it is not clear that patients would consider the greater frequency (daily versus thrice weekly) and higher maximum number of applications (56 versus 48) to represent "a simplified dose schedule." Most importantly, the absence of within-trial dose-response data denies prescribers and patients the critical information about safety and effectiveness that they need to make an informed decision as to which of the applicant's two strengths of imiquimod cream (and corresponding dose regimens) to prescribe and use for the treatment of EGW. I am not aware of any recently-approved drug products indicated for the treatment of a sexually transmitted disease, or even for an infectious disease², for which multiple regimens for the same dosage form are recommended in labeling in the absence of safety and efficacy data for both strengths obtained within the same trial.

¹ *Sexually Transmitted Diseases Treatment Guidelines, 2010*; MMWR; vol 59; Dec 17, 2010.

² Levaquin is an example of a drug, indicated for an infectious disease, which has two dosing regimens for the same dosage form and indication supported by efficacy data obtained from an active-controlled trial using both regimens in separate arms.

Per 21CFR314.50(d)(5)(v), “[e]vidence is...required to support the dosage and administration section of the labeling, including support for the dosage and dose interval recommended.” For a new molecular entity, a new indication, or even a new dosage form, this data would typically be obtained early in development, and used to select the dose that would be developed for marketing. For a new strength of a drug that is already marketed by an applicant at a different strength in the same dosage form and for the same indication, this support would include information about the safety and efficacy of the proposed dose relative to the marketed dose. In the case of imiquimod cream 3.75%, the applicant was informed that data for their marketed imiquimod 5% cream product and the propose imiquimod 3.75% cream product obtained from well-controlled trials would be needed to support the new dosage and dose interval and to inform labeling.

Dose range finding data was included in the initial application for imiquimod 5% cream. A clear dose-response was seen with increasing concentration (1% and 5%) for both efficacy and safety, with higher response rates for complete clearance and higher rates of local adverse reactions observed with the 5% concentration compared to the 1% concentration. The applicant (3M at that time) also studied these strengths (1% and 5%) applied daily (in contrast with thrice weekly), using similar enrollment criteria and endpoints as used in their pivotal trials with thrice weekly application; efficacy rates were similar to those observed with thrice weekly application, but local adverse events were higher³, and only the thrice-weekly regimen with the 5% strength was approved. This information, combined with the dose-response also seen with the 2.5% and 3.75% strengths, suggests that in the absence of evidence to the contrary, the lower strength and daily regimen proposed in this application will be less effective (but perhaps not more safe) than the marketed strength and thrice-weekly regimen.

To obtain marketing approval, applicants need to demonstrate the effectiveness of their products through the conduct of adequate and well-controlled studies. Generally in these studies the applicant’s product is compared to placebo or vehicle. In the case of sexually transmitted diseases, however, the Agency has stated that because such diseases are contagious and pose serious consequences to the health of others, it may be important to consider whether a new product is less effective than available alternative therapies⁴. EGW are a sexually transmitted disease which can pose serious consequences to the health of others, the treatment of which likely reduces both infectivity and viral DNA load. No data were presented to demonstrate that this disease is not sexually transmitted, does not have serious consequences to the health of others, or that the transmission or consequences are not impacted by treatment. Hence inadequate evidentiary support for the recommended dose and dosing regimen presents a safety concern because a less effective dosing regimen could result in greater transmission of EGW and its etiologic agent, HPV, with the attendant public health risks and potentially serious consequences to the health of others.

3. CMC

The drug product, Zyclara (imiquimod) cream, 3.75%, is the same as that approved under NDA 22-483 on March 25, 2010. With the exception of stability data for a single batch of the

³ Medical Officer’s Review, NDA 20-723; Stanka Kukich, MD; archived 3.3.97

⁴ Federal Register Vol 60 No 147 pp39180-1.

product, apparently all data contained in the CMC section was previously submitted to NDA 22-483. There are no changes in the chemistry, manufacturing, and controls, and no change in expiry dating. Facilities inspections are completed and acceptable.

The formulation of the drug product is essentially identical to the applicant's other marketed imiquimod cream, Aldara, differences between the two products being limited to the concentration of the active ingredient (3.75% and 5%, respectively) and the concentrations of water (b) (4) and (b) (4), respectively) and isostearic acid (b) (4) and (b) (4)). The latter difference represents a Level 1 change under SUPAC-SS⁵.

Dr. Shulin Ding found that the NDA contained sufficient information to assure the identity, strength, purity and quality of the drug product, and recommended *Approval* from a CMC perspective.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical studies were submitted to NDA 201153; the applicant provided cross-reference to the nonclinical studies in NDA 22-483.

Previously-identified nonclinical findings include occurrence of immune system exhaustion leading to immunosuppressive effects with long-term systemic exposure to imiquimod, and vehicle-associated skin papillomas and enhanced UVR-induced skin tumor formation, and embryofetal toxicity in rats.

Dr. Jianyong Wang recommended *Approval* of this application, pending changes to the Pregnancy section of labeling to reflect the lower multiples of exposure (for those values based on AUC) obtained using human pharmacokinetic data from subjects with external genital warts.

5. Clinical Pharmacology/Biopharmaceutics

The applicant's product is a topical cream containing 3.75% imiquimod; the proposed dose regimen for treatment of external genital and perianal warts is up to one packet applied daily until clearance or for up to 8 weeks, whichever occurs first.

The applicant conducted a pharmacokinetic study (GW01-0804) under maximal use conditions (up to one packet applied once daily for 3 weeks) in 18 subjects (13 men, 5 women) with ≥ 8 warts (mean 23.78) or with a total wart area of involvement $\geq 100\text{cm}^2$ (mean 108.33). The mean time to reach the maximum serum concentration (t_{max}) in subjects with EGW was 12 hours. The mean half-life ($t_{1/2}$) of imiquimod was 12.4 ± 8.2 hrs on Day 1 and 24.1 ± 12.4 hrs on Day 21. The mean peak serum imiquimod concentration (C_{max}) at the end of week 3 was 0.488 ng/mL, and AUC_{0-24} was 6.975 ng-hr/mL.

⁵ Email communication to author from Shulin Ding, PhD, dated 11.19.10, 10:40am.

The applicant has an outstanding postmarketing requirement, communicated at the time of original approval of NDA 22-483, to, “[c]onduct a randomized crossover clinical trial (Zyclara Cream, 3.75% vs. vehicle) in patients with actinic keratosis to detect treatment-related change in atrial ectopy;” the applicant submitted a protocol in response to this requirement, which is under review.

Dr. E. Dennis Bashaw found that the applicant met the requirements of CFR 320, and recommended *Approval* of the application from a Clinical Pharmacology standpoint.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

During the development program for external genital warts, the applicant interacted with the Agency on the following occasions:

- Guidance meeting, July 27, 2007
- End-of-Phase 2 meeting, January 20, 2008
- Guidance teleconference, May 20, 2008
- PreNDA meeting, November 18, 2009
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No Special Protocol Assessment was requested or performed, and no agreement letter was issued.

The Agency consistently recommended that the applicant identify the dose (concentration and dosing regimen) that optimizes the risk-benefit profile for imiquimod cream. The applicant was advised to provide data that would allow comparison of efficacy and safety for the product/s in development and the marketed product (Aldara 5% cream) (b) (4)



In a letter dated 23 May 2008, the Agency articulated the following:

Assuming positive and significant study outcomes as well as a better or unchanged safety profile, the application should include information to demonstrate why the results for the proposed imiquimod treatment regimen represent an appropriate labeling change for the product. Graceway assumes a risk that in the face of equivocal or borderline significance this may not be possible without comparative data between the regimens. In addition, it would not [be] possible to label the product for multiple treatment regimens

without adequate data to convey information supporting the treatment decisions healthcare practitioners would have to make.

The applicant submitted data from two identically-designed pivotal trials, Study GW01-0801 and Study GW01-0805 (hereafter 801 and 805, respectively), to establish the effectiveness of their product applied daily for up to 8 weeks in the treatment of external genital warts. Both trials were multi-center, prospective, randomized, double-blind, parallel-group studies with three arms: 2.5% imiquimod, 3.75% imiquimod and vehicle; neither study included an arm for the marketed strength (5%). The population enrolled were subjects 12 years of age and older with 2 to 30 external genital/perianal warts involving an area of at least 10mm².

The study design for 801 and 805 differs from that of study 1004-IMI, the pivotal trial for imiquimod 5% cream described in labeling, in the following ways:

	801/805	1004-IMI
Inclusion criteria	2-30 warts	2-50 warts
Primary endpoint	Complete clearance of all warts, baseline and new	Complete clearance of baseline/target warts
Primary timepoint	8 weeks after EOT (≤ 16 wks)	At EOT (≤ 16 wks)

Sources: Statistical Review and Evaluation, NDA 20-723; Paul Flyer, PhD; archived 5.9.97, p.1. Also NDA 201153

These differences, in addition to the fact that these are separate studies, disparate in time, make comparison of safety or efficacy results between the 3.75% formulation and the marketed 5% formulation fraught.

For studies 801/805, the primary efficacy measure was wart count. The primary efficacy endpoint was complete clearance rate, defined as the proportion of subjects with complete clearance of all warts, baseline and new, in all anatomic areas. The primary timepoint was the End-of-Study (EOS) visit, which occurred 8 weeks after end of treatment (EOT), hence ≥ 16 weeks. EOT occurred at week 8 or complete clearance, whichever occurred first. The efficacy results are presented in the table below.

Complete Clearance Rates at EOS, Intent-to-Treat (ITT) and Last Observation Carried Forward (LOCF)

	Imiquimod 3.75% cream	Imiquimod 2.5% cream	Vehicle cream
Study 801	27% (53/195)	19% (34/178)	10% (10/97)
p-value vs vehicle	0.001	0.065	
Study 805	29% (60/204)	25% (50/202)	9% (9/105)
p-value vs vehicle	<0.001	0.001	

Source: adapted from Statistical Review and Evaluation, NDA 201153 (ref to 22483); Kathleen Fritsch, PhD, archived 10.04.10, p.11.

Imiquimod 3.75% cream was superior to vehicle in both studies in the proportion of subjects that achieved complete clearance of their external genital warts in all anatomic areas at the primary timepoint (EOS, or 8 weeks following EOT). A dose-response is observed, with the

response rate for the 3.75% arm exceeding that of the 2.5% arm in both studies. The applicant is not seeking approval of Zyclara 2.5% cream for the treatment of external genital warts.

Efficacy results varied by sex, with higher response rates seen in women. Subgroup analysis of complete clearance rates by sex is presented in the following table.

Complete Clearance Rates by Sex

Study	Sex	imiquimod 3.75% cream	imiquimod 2.5% cream	Vehicle cream
801	Male	20% (19/95)	13% (11/83)	4% (2/47)
	Female	34% (34/100)	24% (23/95)	16% (8/50)
805	Male	17% (15/88)	15% (13/85)	4% (2/49)
	Female	39% (45/116)	32% (37/117)	13% (7/56)

Source: adapted from Statistical Review and Evaluation, NDA 201153 (ref to 22483); Kathleen Fritsch, PhD; archived 10.04.10, p.13.

For both studies and all arms, the median duration of therapy was 8 weeks, making the median duration to primary timepoint (EOS visit) 16 weeks. For the active (3.75%) arm, the median days of therapy was 48 days in study 801 and 50 days in study 805, and the median number of packets used was 48 (both studies). Of note, in a pivotal study of the marketed imiquimod 5% cream (IMI1004), the median duration of therapy and the median duration to the primary timepoint (primary timepoint was at end of treatment) was 10 weeks overall and 8 weeks for women, and maximum number of packets used/days of treatment was 48⁶. For the pivotal studies presented in this application, complete clearance rate at EOT was lower than at EOS for both active and vehicle in both studies, as seen in the table below.

Complete Clearance Rates at End of Treatment and End of Study, ITT, LOCF

Arm	Study 801		Study 805	
	End of Treatment Median wk 8	End of Study Median wk16	End of Treatment Median wk 8	End of Study Median wk 16
3.75% % n/N	22.1% (43/195)	27.2% (53/195)	15.7% (32/204)	29.4% (60/204)
Vehicle % n/N	5.2% (5/97)	10.3% (10/97)	3.8% (4/105)	8.6% (9/105)

Source: adapted from NDA 201153 NDA, ISE 5.3.5.3.1, pp. 51-55.

The reader is referred to the biostatistical and clinical reviews by Dr. Kathleen Fritsch and Dr. Milena Lolic, respectively, for further discussion of the efficacy data.

The applicant did not provide data from any study in which the proposed product (and dosing regimen) was studied with the marketed product, imiquimod 5% cream, as an active control. Because of this, I disagree with Dr. Lolic’s conclusion that the applicant has provided sufficient information to support the dose and dosing regimen proposed for labeling.

⁶ Medical Officer’s Review, NDA 20-723; Stanka Kukich, MD; archived 3.3.97, pp.13-14.

8. Safety

The primary safety database is derived from two pivotal studies, and includes 779 subjects exposed to imiquimod, 400 of whom received 3.75% cream (applied daily for up to 8 weeks) and 379 of whom received 2.5% cream (applied daily for up to 8 weeks). Supportive safety data is provided from a PK study in which 18 subjects were exposed to 3.75% cream for 3 weeks. The safety database is adequate.

There was one death in the development program: a 40 year old subject died on day 40 from a gun shot wound; this event appears not to be treatment-related. In the pivotal trials, there were 17 serious adverse events (SAE) in 12 subjects, 11 events in 7 subjects in the 3.75% group, 5 events in 4 subjects in the 2.5% group, and 1 event in 1 subject in the placebo group. All of the SAEs were considered unlikely to be related to study drug by investigators, as well as by Dr. Lolic.

Adverse events (AE) were reported for 41% of subjects in each of the active arms and in 34% of the subjects receiving vehicle. The most common AEs were local site reactions, headache, and upper respiratory infections. Local site reactions were more frequent and more severe in the 3.75% group vs the 2.5% group, and both groups exceeded rates for the vehicle group. There was no arm treated with imiquimod 5% cream in either pivotal trial, so no comparison can be made between the proposed new dosing regimen and the approved dosing regimen. Collection of adverse event data and assessment of local tolerance did not reveal unexpected safety signals.

In addition to routine adverse event collection, local site reactions were actively assessed at each visit. Local site adverse reactions are recognized and expected with topical imiquimod use. However, these reactions are of particular concern on the genital skin in the treatment of external genital warts because disruption of the genital skin and mucosa from any cause may increase the risk for infection with other sexually transmitted diseases. The rates of local skin reactions as actively assessed by the investigator are presented in the following table:

Frequency Distribution of Post-Baseline Local Skin Adverse Reactions

Any reaction % (n)	Imiquimod 3.75% cream	Vehicle cream
Severe reaction % (n)	N 400	N 202
Any edema	41% (163)	8% (16)
Severe edema	2% (8)	0
Any erythema	70% (280)	27% (55)
Severe erythema	9% (36)	1% (1)
Any flaking/scaling/dryness	30% (118)	10% (21)
Severe flaking/scaling/dryness	0	0
Any exudate	34% (135)	3% (5)
Severe exudate	2% (7)	0
Any scabbing/crusting	23% (93)	4% (8)
Severe scabbing/crusting	1% (3)	0
Any erosion/ulceration	36% (143)	5% (9)

Severe erosion/ulceration	11% (43)	1% (1)
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Source: adapted from Clinical Review NDA 201153, Milena Lolic, MD; archived 10.29.10. p.60.

Of particular concern are exudate, scabbing/crusting, and erosion/ulceration, as these reaction patterns may indicate impaired integrity of the cutaneous/mucosal barrier. Thirty-six percent of subjects experienced erosion/ulceration, which by definition indicates impairment of barrier integrity. Disruptions of the cutaneous/mucosal barrier may place patients at an increased risk for infection by other sexually transmitted pathogens. Because the applicant did not include an arm for treatment with their marketed imiquimod cream product, it is not possible to compare the magnitude or rates of these (or any) adverse reactions between the two strengths of their imiquimod cream products. Of note, however, the rate of erosion/ulceration (safety population) was approximately two-fold greater than the rate of complete clearance in subjects treated with imiquimod 3.75% cream applied daily, whereas the rate of erosion plus ulceration (assessed independently) was less than the rate of complete clearance in subjects treated with imiquimod 5% cream applied thrice weekly.

An additional safety concern is the potentially reduced efficacy of the proposed dose and dose regimen, with the consequent risk of increased transmission of EGW and its etiologic agent, HPV, with the attendant public health risks and serious consequences for the health of others.

I disagree with Dr. Lolic's conclusion that the applicant has provided sufficient data to support the safety of the dose and dose regimen and proposed labeling.

9. Advisory Committee Meeting

The application was not presented at an Advisory Committee meeting. Imiquimod is not a new molecular entity; a 5% concentration of the drug product is approved for this indication. Review of the application did not identify novel issues which would merit Advisory Committee input.

10. Pediatrics

The applicant requested a partial waiver for the pediatric age group less than 12 years of age because the necessary studies would be highly impractical based on the small number and geographical dispersion of patients with psoriasis in that age group. The applicant completed studies with their product in patients 12 years of age and older, including adults.

The efficacy of imiquimod 3.75% cream in pediatric patients aged 12 years and older could be extrapolated from adult data because, although disease prevalence varies with age, the pathophysiology is understood to be the same in adolescents and adults. Additionally, there are not known age-related factors that would make the disease either more or less responsive to treatment in adolescents than adults.

The pivotal trials and the PK study allowed for inclusion of subjects 12 years and older; however, enrollment was limited to 3 subjects in the pivotal trials and one subject in the PK study. Supportive pediatric safety data includes the AERS database for imiquimod 5% cream

(indicated for the treatment of external genital warts in subjects 12 years of age and older), and safety data from studies conducted in accordance with a Pediatric Written Request in pediatric subjects aged 2 to 2 years of age with molluscum contagiosum. Safety data generated in adult subjects is also supportive. Consultation was obtained from the Pediatric and Maternal Health Staff, who found the direct and supportive data sufficient to allow for a finding of safety in subjects 12 years of age and older with external genital warts.

The application was presented to the Pediatric Review Committee (PeRC) on 29 September 2010. The PeRC concurred with the Division's position that the applicant's request for a waiver should be granted for patients younger than 12 years of age. The PeRC agreed that efficacy data was not needed in pediatric adolescent subjects, but could be extrapolated from adequate adult data, and that the application contained adequate data for a determination of safety.

11. Other Relevant Regulatory Issues

DSI audits were not requested.

12. Labeling

All components of labeling, including carton and container labels, professional (package insert) and patient labeling, were reviewed. Negotiations with the applicant are ongoing at the time of close of this review.

I do not find that the applicant has provided sufficient information to inform product labeling. In the absence of within-trial safety and efficacy information for both strengths of their topical imiquimod cream products in the treatment of external genital and perianal warts, prescribers and patients will not have critical information needed to select the dose for the treatment of patients with this sexually transmitted disease.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action: *Complete Response*

The applicant has not provided evidence to support the new dose (3.75%) and dose interval (apply daily for up to 8 weeks) for their proposed imiquimod cream product. Hence, there is insufficient information about the drug to determine whether the product is safe for use under the conditions proposed in the submitted labeling.

Recommended Comments to Applicant:

Conduct an active- and vehicle-controlled trial of the safety and efficacy of the proposed 3.75% strength and the marketed 5% strength of imiquimod cream in the treatment of EGW.

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/s/

JILL A LINDSTROM
02/02/2011